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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/063,519
Filing Date: May 01, 2002
Appellant(s): GODDARD ET AL.

Daniel Hart
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 06 December 2005 appealing from the Office action mailed 05 July 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention (item no. 9 beginning at page 8 of the Office Action mailed 1/31/2005).

(7) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Prior Art of Record

Hu et al., Analysis of genomic and proteomic data using advanced literature mining. Journal of Proteome Research, 2003 Jul-Aug; 2(4):405-412 (PTO-892 mailed 1/31/05).

Haynes et al., Proteome analysis: biological assay or data archive? Electrophoresis, 1998 Aug; 19(11):1862-1871 (PTO-892 mailed 1/31/05).

Pennica et al., *WISP* genes are members of the connective tissue growth factor family that are up regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors. Proc. Natl. Acad. Sci. USA, 1998 Dec; 95:14717-14722 (PTO-892 mailed 1/31/05).

Gokman-Polar et al., Elevated protein kinase C βII is an early promotive event in colon carcinogenesis. Cancer Research, 2001 Feb; 61:1375-1381 (PTO-892 mailed 7/5/05).

First Declaration of J. Christopher Grimaldi (Exhibit 1, filed 5/2/2005).

Second Declaration of J. Christopher Grimaldi (Exhibit 2, filed 5/2/2005).

Declaration of Paul Polakis, Ph.D. (Exhibit 3, filed 5/2/2005).

Bruce Alberts et al., Molecular Biology of the Cell, 3rd ed. (1994) (Exhibit 4, filed 5/2/2005).

Bruce Alberts et al., Molecular Biology of the Cell, 4th ed. (2002) (Exhibit 5, filed 5/2/2005).

Benjamin Lewin., Regulation of transcription. Genes VI, Chapter 29, pp. 847-848 (1997) (Exhibit 6, filed 5/2/2005).

Zhigang et al., Prostate stem cell antigen (PSCA) expression in human prostate cancer tissues and its potential role in prostate carcinogenesis and progression of prostate cancer. World Journal of Surgical Oncology, 2004, 2(13):1-7 (Exhibit 7, filed 5/2/2005).

Meric et al., Translation initiation in cancer: A Novel target for therapy. Cancer Therapeutics., 2002, 1:971-979 (Exhibit 8, filed 5/2/2005).

Gygi et al., Correlation between protein and mRNA abundance in yeast. Mol. Cell. Biol., 1999, 19(4):1720-1730 (Exhibit 9, filed 5/2/2005).

Falb et al. US Patent 6,156,500 (IDS filed 5/2/2005).

Levinson et al. US Patent 6,562,343 B1 (IDS filed 5/2/2005).

Hanash S. [a]., Integrated global profiling of cancer. Nature Reviews, Applied Proteomics Collection, March 2005, pp. 9-14 (IDS reference 9 filed 9/6/05).

Hanash et al [b]., Making sense of microarray data to classify cancer. The Pharmacogenomics Journal, 2003, 3(6):308-311 (IDS reference 8 filed 9/6/05).

(9a) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a substantial asserted utility or a well established utility.

Claims 1-5 are directed to an antibody that binds SEQ ID NO:14. The specification discloses the isolation of a nucleic acid, SEQ ID NO:13, which encodes a

protein, SEQ ID NO:14 which is disclosed as PRO1864 (see Figure 13 and 14). The DNA of SEQ ID NO:13 is disclosed to be over expressed in melanoma vs. normal skin but the protein is not disclosed to be expressed (see page 141).

The specification does not disclose that the polypeptide has any homology with known, characterized polypeptides. The instant specification does not disclose any additional information regarding PRO1864 such as subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO1864, and what physiological significance PRO1864 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

The specification generally asserts that all of the disclosed PRO polypeptides will be useful for a number of purposes, however, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial. The asserted utilities will each be addressed in turn.

1) the PRO polypeptide can be used to isolate other polypeptides to which it binds (paragraph 0329): This asserted utility is not specific or substantial. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides. Furthermore, since the specification does not disclose how PRO1864 or its binding partners can be used, significant further research would be required of the skilled artisan to determine how to use the claimed polypeptide or its binding partner. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

2) the PRO polypeptide can be used as a molecular weight marker (paragraph 0334): This asserted utility is not specific. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides.

3) the PRO polypeptide can be used in tissue typing (paragraph 0336): This asserted utility is not specific or substantial. With the exception of a few housekeeping genes, all polypeptides have a tissue specific pattern of expression, and thus virtually any polypeptide can be used in tissue typing. Thus, the asserted utility is not specific to PRO1864.

4) the PRO polypeptide can be used in therapy (paragraph 0337): This asserted utility is not specific or substantial. Since a defect in any polypeptide is likely to cause a disease of some sort, every polypeptide is a target for drug development. Thus, the asserted utility is not specific to the claimed PRO1864 polypeptide. Furthermore, the specification does not disclose a nexus between any specific disease states and a change in amount or form of PRO1864. Significant further research would have to be conducted to identify such a nexus. Therefore, the asserted utility is not substantial.

5) the PRO polypeptide can be used to identify agonists or antagonists (paragraph 0345): Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides. Furthermore, since no activity has been assigned to PRO1864, the assays cannot be conducted until the specific biological activities of PRO1864 are determined empirically. Therefore, the asserted utility is also not substantial.

The specification also discloses that PRO1864 tested positive in a microarray analysis to detect over-expression of PRO polypeptides in cancerous tumors (Example 18, pp. 140). This information does not provide a credible, specific and substantial utility for PRO1864 nucleic acids, polypeptides or antibodies. PRO1864 mRNA levels are indicated as being over-expressed in melanoma tumor as compared to a normal skin. The data is not presented to indicate such overexpression or how it was determined. This is very vague, and does not disclose what mathematical calculations were used to establish significance. Therefore, the data presented in the microarray assay are preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. Clearly, further research would be required of the skilled artisan to establish whether and how a probe used in the microarray assay could be used as diagnostic markers or therapeutic targets. Such further experimentation indicates that the asserted utility is not in currently available form.

Furthermore, the literature indicates that such results are to be evaluated very critically. For example, Hu et al (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant

correlation between expression level and a published role in the disease (see discussion section).

Finally, increased transcription does not always correlate with increased polypeptide levels. See Haynes et al. (1998, Electrophoresis 1921862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes et al concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that increased transcription results in increased polypeptide levels.

Thus, the proposed use of the PRO1864 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[I]t is not a reward for the search, but compensation for its successful conclusion."

Therefore since the polypeptide of SEQ ID NO:14 has no substantial utility, the antibody to SEQ ID NO:14 also does not have a substantial utility.

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10a) Response to Argument

Rejection of claims 1-5 under the utility requirement of 35 USC §101

At the middle of page 4 of the Brief, Appellants argue that the asserted patentable utility of PRO1864 polypeptide is based on the disclosure in Example 18 of the instant application that the mRNA encoding the PRO1864 polypeptide is more highly expressed melanoma tumor compared to normal skin. From the bottom of page 6 to the top of page 8 of the Brief, Appellant, citing case law and MPEP, reviews the legal standard for utility, with which the Examiner takes no issue.

Beginning at page 8 of the Brief, Appellants argue the differential expression of PRO1864 mRNA was detected using well-established technique of quantitative PCR amplification of cDNA libraries isolated from different human normal and tumor tissues samples. To ensure that equivalent amounts of nucleic acid were used in each reaction, the cDNA for β-actin was used as a control. Appellants argue that identification of the differential expression of a PRO polypeptide-encoding mRNA in one or more tumor tissues as compared to one or more normal tissues of the same tissue type "renders the molecule useful diagnostically before the determination of the presence or absence of tumor in a subject suspected of possessing a tumor." It is

further asserted that because it is well established that changes in mRNA levels lead to changes in the level of the encoded protein, one would expect the PRO1864 protein to be differentially expressed in melanoma tumor compared to normal skin. Appellants argue that anti-PRO1864 antibodies may be used in diagnostic assays for PRO1864 (polypeptide), e.g., detecting its expression (and in some cases, differential expression) in specific cells, tissues or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases. Appellants assert that taken together, the specification clearly discloses the "real world" use of the claimed antibodies as diagnostic tools for cancer, particularly melanoma tumors.

Appellants arguments have been fully considered but are not found persuasive for the following reasons. An assay using PCR amplification as described in Example 18, the Appellants merely measure the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO:14. There is no evidence regarding whether the level of PRO1864 polypeptide of SEQ ID NO:14 is more highly expressed in melanoma compared to normal skin. There is insufficient information or experimental data presented on whether the polypeptide or the antibodies binding such (SEQ ID NO:14) of the present invention can serve as a reliable diagnostic marker for melanoma tumor. Moreover, the assay does not establish a causative link between the polypeptide (or antibodies) of the present invention and melanoma tumor. Without such critical information, one skilled in the art would not be able to use the polypeptide of the

present invention as a therapeutic target for treatment of melanoma tumor without undue experimentation. The information disclosed in the instant specification is preliminary at best as there is no evidence or data that a change in PRO1864 mRNA or polypeptide expression is tumor-dependent, consistent and measurable. Finally, the art indicates that the changes in mRNA expression do not correlate with polypeptide levels (e.g., Hu et al, Haynes et al, Gygi et al and Gokman-Polar et al, evidence of record). Clearly further research would be required to reasonably confirm the real world context of the asserted utility, i.e., whether the PRO1864 polypeptide or antibodies binding the polypeptide can serve as a reliable diagnostic marker for melanoma tumors or as a therapeutic target for treatment of melanoma tumors. Accordingly, the claimed utility is not substantial.

Appellants assert that to establish a *prima facie* showing that the claimed subject matter lacks utility, the Examiner must "provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility" (see top of page 10 of the Brief). Appellants claim that the Examiner has issued first Office Action, a final Office Action and an Advisory Action during the prosecution of the instant application. In addition, it is asserted that none of these papers provide any evidence that one of ordinary skill in the art would reasonably doubt the asserted utility. At pages 11-12 of the Brief, Appellants criticize the Examiner's assertions as being unsupported by any facts, evidence or reasoning and claim the Examiner has failed to establish a *prima facie* showing that one skilled in the art would reasonably doubt the asserted utility and directs the Board to accept Appellants disclosed utility as sufficient (top of page 12 of

the Brief). In contrast to Appellants assertions, the Examiner did provide the art of Hu et al and Haynes et al in the first Office Action dated 1/31/05 and the art of Gokman-Polar et al in the final Office Action dated 7/5/05 (discussed in pages 4-5 of the Office Action), which report facts, and provide evidence of a lack of a correlation between mRNA expression and corresponding polypeptide expression. Additionally, Appellants submitted the art of Gygi et al with the response dated 5/2/05 and the art of Hanash [a] and Hanash et al [b] on the IDS dated 9/6/05 (all discussed in more detail below), which provide additional facts and evidence of a lack of a correlation between mRNA expression and corresponding polypeptide expression in healthy tissue (Haynes et al, Gygi et al) and cancerous tissue (Hu et al, Gokman-Polar et al, Hanash [a] and Hanash et al [b]).

At the middle of page 10 of the Brief, Appellants assert that the Examiner states that the specification discloses that the PRO1864 polynucleotide is more highly expressed in melanoma compared to normal skin, and that Applicants have asserted the use of the molecule for diagnosis (middle of page 10 of the Brief). Further it is asserted the Examiner has rejected this utility, stating that "the examiner cited numerous art that did show mRNA does not correlate with protein" (see Final Office Action at page 4).

The Examiner initially rejected this utility because of the insufficiency of data presented in Example 18. The Examiner argued that there is no supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also significantly differentially expressed in normal tissues compared to their tumor

tissue counterparts, and as such one of skilled in the art would conclude that it is not supported by a substantial asserted utility or a well-established utility. Although, the specification claims that the polynucleotide is more highly expressed in melanoma tumor compared to normal skin, the specification does not teach what is the normal level of expression, does not indicate how high the expression level is compared to, for example, melanoma tumor; and does not provide a statistical correlation to the level of expression (for example, there is no indication of how many samples were compared to study the expression). Furthermore, even if the tumor is malignant, the specification does not describe the type or kind of tumor present in skin tissues. Without knowing the identity of the melanoma, one of skill in art cannot use the polypeptides for diagnosis or therapeutic purposes as asserted. The specification does not disclose a correlation between any specific disorder and the altered level or form of the claimed PRO1864 polypeptide of SEQ ID NO:14. Also, the specification does not predict whether the PRO1864 polypeptide would have high or low expression in a specific, diseased tissue (i.e., melanoma) compared to the healthy tissue control. In addition, the specification does not teach or describe the function or biological significance of this yet to be identified polypeptide (see page 4 of the Office Action dated 1/31/05). Hu et al, (2003), cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see pages 6-7 of the Office Action mailed 1/31/05).

Secondly, the Examiner argued, polypeptide levels cannot be accurately predicted from mRNA levels (Haynes et al, Gygi et al (submitted by Appellant 5/2/05)

and Gokman-Polar et al). See final Office Action dated 7/5/05, pages 4-5. Thus, the Examiner concluded that "further research needs to be performed to determine whether the decrease or increase in PRO1864 cDNA expression compared to normal skin tissue supports a role for the polypeptide in the cancerous tissue (page 7 of the final Office Action dated 7/5/2005). The Appellants assert that based on the above arguments, the Examiner has not established a *prima facie* case lacking utility for claims 1-5 directed to the antibodies (page 11 of the Brief). Appellants also assert that with the exception of the specific references cited by the examiner (Hu et al, Haynes et al and Gokman-Polar et al), the Examiner's assertions are not supported by any facts, evidence or reasoning (Brief at of page 11). It is further argued that these references do not support the Examiner's position. Appellants assert that there is simply no evidence on the record to support the Examiner's assertion that the asserted utility is not substantial, and that the invention is incomplete. Appellants thus conclude that the Examiner has failed to establish a *prima facie* showing that one skilled in the art would reasonably doubt the asserted utility and directs the Board to accept Appellants disclosed utility as sufficient (top of page 12 of the Brief). In contrast to Appellants assertions, the Examiner did provide the art of Hu et al and Haynes et al in the first Office Action dated 1/31/05 and the art of Gokman-Polar et al in the final Office Action dated 7/5/05 (discussed in pages 4-6 of the final Office Action), which report facts, and provide evidence of a lack of a correlation between mRNA expression and corresponding polypeptide expression. Additionally, Appellants submitted the art of Gygi et al with the response dated 5/2/05 as well as the art of Hanash [a] and Hanash et al [b] on the IDS dated 9/6/05, which

provide additional facts and evidence of a lack of a correlation between mRNA expression and corresponding polypeptide expression in healthy tissue (Haynes et al, Gygi et al) and cancerous tissue (Hu et al, Gokman-Polar et al, Hanash [a] and Hanash et al [b]).

From page 12-16 of the Brief, Appellants refer to the declaration of Mr. Grimaldi filed under 37 CFR 1.132 (02 May 2005) and argue against the Hu et al reference. Appellants quote from paragraphs 6 and 7 of the declaration stating that "semi-quantitative analysis employed to generate the data of example 18 is sufficient to determine if a gene is over or under expressed in tumor cells compared to corresponding normal tissue". Further it is asserted by Mr. Grimaldi that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Mr. Grimaldi also asserted that, if a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, i.e., to screen samples to differentiate between normal and tumor".. It is further asserted that PTO's assertions are contradicted by Mr. Grimaldi's statement, "the precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." Appellants assert that this declaration makes clear that since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, how high the level of expression is in normal tissue is irrelevant (see middle of page 13 of the Brief). Further, Appellants argue that Mr. Grimaldi states that if a difference is detected using

these techniques, "this indicates that gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes." Thus, Appellants contend that it is the uncontested opinion of an expert in the field that the results are reliable enough to indicate that the claimed antibodies are useful as diagnostic tools. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a approximately 2-fold amplification of the message amplification (as suggested by the declaration) encoding PRO1864 is significant. However the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease.

However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The specification fails to disclose any specific "fold amplification" that is required between normal and cancerous tissue for a diagnostic determination. Is a 1-fold, a 5-fold, a 10-fold, or a 100-fold difference required? If the "fold amplification" were disclosed in the specification to be 100-fold, for example, then the cDNA that encodes the PRO1864 polypeptide would likely have a specific and substantial utility as a diagnostic marker for melanoma tumors. However, such is not the case here. Most importantly, an assay using cDNA analysis as described in Example 18 merely measures the mRNA level; the chemical intermediate involved in translating DNA into protein and tracking this middle step reveals nothing about protein function, the abundance of protein in a cell, and modifications to proteins after they are produced – changes that may be critical in the development of diseases. Importantly, Example 18 does not measure the over-expression of the PRO1864 polypeptide of SEQ ID NO:14 or antibodies that bind to the polypeptide of SEQ ID NO:14. Regarding the interest of the expert in the outcome of the case, it is also noted that the expert has interest in the outcome of the case, since Mr. Grimaldi is listed as an inventor and is employed by the assignee.

Beginning at the fourth paragraph of page 14 of the Brief, Appellants criticize the publication of Hu et al and claim that the observations of Hu et al are due to the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in

less-prevalent (and, therefore, less studied) ER-negative tumors, citing a statement from the article (3rd paragraph of left column of page 412) as evidence. Thus, it is the contention of the Appellants that because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially expressed gene exists. Further, Appellants argue that Hu et al do not say that a correlation in their study means that genes with less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer. Appellants' arguments have been fully considered but are not found persuasive for the following reasons. Hu et al teach that their study has two implications. First, a careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change. Second, any genes with 10-fold change or more are likely to related be to breast cancer and warrant attention (2nd paragraph of left column of page 412). Hu et al teach that it is likely that this threshold will change depending on the disease as well as the experiment (2nd paragraph of left column of page 412). Hu et al states clearly: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful" (bottom of right column of page 411). Hu et al further states: "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page

405). In addition, Hu et al comprehensively summarized and estimated the relative strengths of all human gene-disease relationship in Medline, and analyzed a microarray expression dataset comparing breast cancer and normal breast tissue in the context of existing knowledge (see, e.g., Abstract of Hu et al.). While it is true that "relationship established by frequency of co-citation do not necessarily represent a true biological link", as Hu et al stated, "it is strong evidence to support a true relationship" (1st paragraph of right column of page 411). Further, while some functional molecules are not included in the analysis, a sample size of 2286 genes is sufficient to validate the author's conclusion. The purpose of a statistical analysis is to predict the property or behavior of the overall population based upon analysis of a sample of the population. In view of the limited disclosure in the instant case, lack of disclosure of the "fold amplification" that was used to determine whether a higher expression, i.e., "more highly expressed" was significant, lack of the statistical analysis, and lack of establishment of a correlative link between gene expression and protein level or a causal link between mRNA expression and melanoma tumour, the teachings of Hu et al support the PTO's position that further research is needed to reasonably identify or confirm a substantial utility for the instantly claimed polypeptide of SEQ ID NO:14 (PRO1864) and the antibodies binding the polypeptide.

Appellants argue that the lack of a known role for PRO1864 in cancer does not prevent its use as a diagnostic tool for cancer (see page 15 of the Brief). Although, the utility is credible and specific it is not substantial. Appellant cites the PTO's written policies, which recognize that the utility of a nucleic acid does not depend on the

function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state: "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridises near a disease-associated gene or it has a gene regulating activity. " (Federal Register, Volume 66, page 1095, Comment 14). This has been fully considered but is not found persuasive. In the instant case, the instant claims are drawn to PRO1864 antibodies where the specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed PRO1864 polypeptide. Appellants quote from M.P.E.P. § 2107 regarding the requirement for a substantial asserted utility. Appellant argues that they have demonstrated at least one reasonable use for the PRO1864 polypeptide as a diagnostic marker for cancer. It is asserted that the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public. This has been fully considered but is not found to be persuasive. M.P.E.P. § 2107 I states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO1864 polypeptides or antibodies binding to such are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO1864 polypeptide or the antibodies binding to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of the PRO1864 polypeptide

between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) cDNA is "more highly expressed" in melanoma compared to normal skin (2) increased mRNA levels do not reliably correlate with increased polypeptide levels (Hu et al, Gokman-Polar et al, Haynes et al, Gygi et al, Hanash [a] and Hanash et al [b]). In view of this, the skilled artisan would have viewed the cDNA amplification results as preliminary with respect to the utility of the encoded polypeptides or the antibodies binding the polypeptide, and would have had to experiment further to reasonably confirm whether or not PRO1864 polypeptides or antibodies binding to the polypeptide PRO1864 (SEQ ID NO:14) can be used as a cancer diagnostic agent.

At page 16 of the Brief, Appellants contend that the data in Example 18 and the first Grimaldi declaration are therefore sufficient to establish the asserted utility, and that the Examiner has not rebutted the presumption of utility that the Appellants' application is afforded. Further Appellants contend that Mr. Grimaldi is an expert in the field who conducted or supervised the experiments at issue and his declaration is based on personal knowledge of the relevant facts at issue. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not cDNA amplification is predictive of increased protein levels. (2) It is important to note that the instant specification only

discloses cDNA amplification data for PRO1864 (i.e., data regarding amplification of PRO1864 mRNA), and does not disclose any information regarding PRO1864 polypeptide levels or antibodies binding the PRO1864 polypeptide. Furthermore, there is strong opposing evidence showing that mRNA amplification is not predictive of protein levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Haynes et al., discussed below. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Mr. Grimaldi is named as one of the inventor and is employed by the assignee. (4) Finally, Mr. Grimaldi refers to facts; however, the data is not included in the declaration so the examiner could not independently evaluate them. There is no protein data. In conclusion, the Examiner submits that based on consideration of the evidence as a whole, the rejection is proper.

Beginning at page 17 of the Brief, Appellants argue that Gokman-Polar et al, Haynes et al, and Gygi et al, do not refute Appellants assertion that a change in mRNA levels leads to a corresponding change in the level of the encoded protein. Contrary to Appellants assertion that Gokman-Polar et al does not contradict the utility and enablement of the instant claims, as noted by Appellant at page 17 of the Brief, Gokman-Polar et al states that "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level." (Final Office Action at page 5). Appellant reviews the data of Gokman-Polar and asserts that with one exception, the trend in the data is

that mRNA and protein levels are positively correlated, supporting Appellants assertion that increased mRNA levels correlate with increased protein levels. Appellant points to Figures 2 and 6 and Figures 4 and 7, to support the assertion that with one exception, the third isozyme, the mRNA levels are positively correlated to protein levels. While protein levels do not increase or decrease in direct proportion to the changes in mRNA, the trend in five of the six examples is that protein levels are positively correlated to mRNA levels. Apellants conclude that this evidence is hardly sufficient to establish that one skilled in the art would reasonable doubt that there is a reasonable correlation between mRNA levels and protein levels. This has been fully considered but is not found persuasive for the following reasons. Gokman-Polar clearly conclude "Our data demonstrate that changes in mRNA levels for individual PKC isozymes do not coincide with alterations in protein expression. Therefore, caution should be used in interpreting quantitative analysis of changes in PKC isozyme mRNA in the absence of information on protein expression." (page 1380, last three lines of right column to top of page 1381). Further, Gokman-Polar indicates that "although the changes in mRNA levels were significant, the dramatic changes in PKC isozyme protein expression could not be explained by transcriptional control alone." and "Other regulatory mechanisms that could contribute to the observed alterations in PKC isozyme expression include changes in message stability or translatability, protein phosphorylation, and protein stability." (see page 1380, right column 2nd to last paragraph). Regarding Appellants criticism of Gokman-Polar as insufficient evidence that one skilled in the art would reasonably doubt that there is a reasonable correlation between mRNA levels and

protein levels, Gokman-Polar et al is cited as one of several pieces of evidence that protein levels cannot be accurately predicted from the level of the corresponding mRNA. The instant specification does not provide information regarding whether or not the PRO1864 polypeptide is "more highly expressed" in melanomas compared to normal skin, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptide and antibody thereto is not in currently available form, the asserted utility is not substantial.

Contrary to Appellants assertion that Haynes et al does not contradict the utility and enablement of the instant claims, Haynes et al states that "These results suggest that even for a population of genes predicted to be relatively homogeneous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA" (page 1863, 2nd paragraph). Appellants contend that Haynes et al did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Haynes et al had studied more than 80 polypeptides relatively homogeneous in half-life and expression level found no strong correlation between polypeptide (steady state) and transcript levels. Appellants assert that Haynes et al reported that they "found a general trend but no strong correlation between protein and transcript levels". However, Appellants assert that inspection of Figure 1 shows clear correlation between the mRNA levels and protein levels measured. Further it is claimed that this correlation is confirmed by an inspection of the full-length research paper from which the data in Figure 1 were derived, (Gygi et al, Molecular and Cellular Biology,

1999, 1720-1730, a reference provided by the Appellants on 5/2/05). Although Appellants assert that there is a strong correlation between mRNA expression and protein expression, Gygi et al conclude that transcript levels provide little predictive value with respect to the extent of protein expression (page 1730, last line). Furthermore, Gygi et al clearly state that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data (see abstract). Appellants contend that Haynes and Gygi et al looked at the static level of mRNA across many genes, not changes in the level of expression for single gene. Thus, Appellant contends that Haynes and Gygi have nothing to do with changes in protein levels resultant from changes in mRNA levels because they did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Appellants appear to be holding Haynes and Gygi to a higher standard than their own specification, which does not provide any information or testing on whether a change in amount or form of the PRO1864 polypeptide correlates with a change in PRO1864 mRNA in melanomas compared to normal skin.

Appellants have failed to establish that there exists a correlation between the mRNA levels and the protein levels of PRO1864 either in steady state or in a dynamic changing environment (i.e., melanoma). Appellants appear to argue that Haynes teaches that there was a general trend but no strong correlation, between protein and transcript levels and there is a positive correlation between mRNA and protein among most of the 80 yeast proteins studied. On the another hand, Appellant argues that the

Haynes et al did not compare mRNA expression levels and protein levels in the same yeast cells and thus the analysis by Haynes et al is not applicable to the present application. Appellant's arguments have been fully considered, but are not found persuasive for the following reasons. First, Appellant ignores the overall teachings of Haynes et al. At the 2nd paragraph of the left column of page 1863, Haynes et al clearly states, "For some genes studied equivalent mRNA transcript level translated into protein abundances which varied by more than 50-fold. Similarly, equivalent steady state protein expression levels were maintained by transcript levels varying by as much as 40-fold". Haynes et al concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, 2nd paragraph, last two lines). Specifically, Haynes et al state, "These results suggest that even for a population of genes predicted to be relatively homogenous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (p. 1863, 2nd paragraph, last five lines). Haynes et al also state, "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a substantial utility. Furthermore, Appellants arguments that Haynes et al did not compare mRNA expression levels and protein levels in the same yeast cells are invalid because Haynes et al clearly sates: "we have determined the correlation of expression at the mRNA and protein levels for a population of selected genes in the yeast *Saccharomyces cerevisiae* growing at mid-log

phase (the 2nd paragraph of left column of page 1863). In addition, Appellant cited the art of Hanash [a] and Hanash et al [b] on the IDS filed 9/6/05, which provide additional corroboratory evidence that polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript. In agreement with the findings and conclusions of Gokman-Polar, Haynes et al and Gygi et al, Hanash [a] states "There is a need to profile gene expression at the level of the proteome and to correlate changes in gene-expression profiles with changes in proteomic profiles. The two are not always linked-numerous alterations occur in protein levels that are not reflected at the RNA level." (see page 12). Further, Hanash [a] indicates that tumors are complex biological systems and no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics (see abstract). Additionally, Hanash et al [b] states "However perfected DNA microarrays and their analytical tools become for disease profiling, they will not eliminate a pressing need for other types of profiling technologies that go beyond measuring RNA levels, particularly for disease-related investigations." (see page 311). In view of the totality of the evidence the skilled artisan would not reasonably presume that the PRO1864 polypeptide is "more highly expressed" in melanoma tumor compared to normal skin based on the disclosure regarding PRO1864 mRNA expression without actually testing for PRO1864 polypeptide expression. The requirement for such testing to reasonably confirm the asserted utility indicates that the asserted utility is not substantial, i.e., it is not in currently available form.

Appellants on page 19 of the Brief Appellants assert that the Examiner has failed to establish a *prima facie* case that one of skilled in the art would doubt Appellants asserted utility. It is asserted by Appellants that the Examiner has relied on essentially two arguments in rejecting the pending claims for lack of utility. First, it is claimed that the examiner has questioned the sufficiency, reliability and significance of the data reported in Example 18 as well as the supporting first Grimaldi declaration. Secondly, it is asserted that the Examiner relied on the references of Gokman-Polar et al, Haynes et al and Gygi et al to support the assertion that the polypeptide levels cannot be accurately predicted from mRNA levels. However, the Examiner in rejecting the pending claims for lack of utility, noted that PCR amplification as described in Example 18, merely measures the mRNA level; it does not measure the over-expression of the PRO1864 polypeptide. There is insufficient information or experimental data presented on whether the polypeptide or antibodies of the present invention can serve as a reliable diagnostic marker for melanomas and there is no statistical analysis of the expression data (mRNA). Moreover, the assay does not establish a causative link between the polypeptide of the present invention and melanomas. Without such critical information, one skilled in the art would not be able to use the molecule of the present invention as a diagnostic marker or as a therapeutic target for treatment of melanomas without further experimentation. Accordingly, the results obtained based upon the assay described in Example 18 only serve as the beginning point for further research on the biological functions or physiological significance of the antibody that binds to the polypeptide of SEQ ID NO:14 (PRO1864) and does not provide a substantial utility for the present

invention. In addition, the Examiner has cited Hu et al that cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Furthermore, the Examiner also pointed to the art of Haynes et al, Gygi et al, as well as the art of Hanash [a] and Hanash et al [b] submitted by Appellant (IDS filed 9/6/05), all of which teach that mRNA levels do not accurately predict protein levels. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

Appellants on page 20 of the Brief Appellants indicate that they have provided sufficient rebuttal evidence (including the first Grimaldi declaration) of utility and also claim that they have established that the gene encoding the PRO1864 polypeptide is differentially expressed in certain cancers (page 21 of the Brief). Contrary to Appellants assertion that the Examiner has not provided any evidence or reasoning to challenge the reliability and significance of the data in Example 18 which reports that the mRNA for PRO1864 is more highly expressed in melanomas compared to normal skin respectively, the Examiner has provided published prior art that (1) cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue and (2) references report that mRNA levels do not accurately predict protein levels. Appellants contend that Grimaldi declaration establishes that it is the opinion of an expert in the field who has personal knowledge of the facts surrounding Example 18 that there is at least a two-fold difference in mRNA for PRO1864 between the tumor tissue and the counterpart normal tissue, and that the PRO1864 genes, polypeptides and antibodies are useful for

differentiating tumor tissue from normal tissue. This has been fully considered but is not found to be persuasive because this appears to be Declarant's opinion, and is not supported by any facts or evidence. There is no description in the specification that would indicate a correlation with higher or lower expression levels of the message to the PRO1864 polypeptide. It remains that; there is no information on the record as to whether the claimed protein is expressed at all in skin tissue, cancerous or otherwise. The specification does not disclose any special feature or prognosis, of melanomas indicating differential expression to distinguish tumor tissue from normal tissue. It is left to the skilled artisan to determine the significance (if any) of such difference. Such constitutes the type of further research required to bestow a substantial utility on the claimed invention, that of the antibodies to the PRO1864 polypeptide.

Appellants contend on page 22 of the Brief (see also pages 28-29 of The Brief) that it is well established in the art that in most cases a change in the level of mRNA for a particular protein leads to corresponding change in the level of the encoded protein. Appellants assert that the second Declaration provided by Mr. Grimaldi supports this assertion. Citing paragraph 5, of the declaration Appellants contend that 'those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed... the gene product or polypeptide will also be over-expressed... This same principle also applies to gene under-expression." At paragraph 4 of the second Grimaldi Declaration, the Declarant discusses mutations of Her2/Neu (c-erbB2), and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and

the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1864 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PRO1864 gene is known to occur. All that the specification demonstrates is that the PRO1864 mRNA acid was more highly expressed in melanoma compared to normal skin tissue. No mutation or translocation of PRO1864 has been associated with melanomas. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PRO1864 polypeptide is amplified in an unknown number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the claimed antibodies binding the polypeptides.

In addition, beginning at page 23 of the Brief (see also page 29 of the Brief) Appellants assert that the declaration submitted by Dr. Polakis asserts that, "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein (at paragraph 6 of the declaration). Appellant argues that it is more likely than not for increased mRNA levels to predict increased protein levels. Appellant presents a Declaration by Dr. Polakis under 37 CFR 1.132 as evidence that mRNA expression correlates well with protein

levels in general. In the declaration, Dr. Polakis states that a primary focus of the tumor antigen project is to identify tumor cell markers useful as targets for diagnosis and treatment of cancer in humans. Dr. Polakis states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis states that approximately 200 genes transcripts are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis states approximately 80% of samples show correlation between increased mRNA levels and changes in the level of protein expressed from that mRNA. Dr. Polakis states that it remains a central dogma in molecular biology that increased RNA levels are predictive of corresponding increased levels of the encoded protein. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. The declaration of Dr. Polakis is insufficient to overcome the rejection of claims 1-5 under 35 U.S.C.§101 and Appellant's argument is not deemed to be persuasive for the following reasons.

First, it is important to note that Dr. Polakis clearly states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis does not state that tumor versus

normal differential tissue expression using PCR amplification analysis alone can establish the use of a polypeptide or the antibodies as a diagnostic marker for a specific tumor. Secondly, Dr. Polakis states approximately 80% of the samples show correlation between increased mRNA levels and changes in the level of protein expressed from that mRNA. However, Dr. Polakis does not state whether the increase in protein level was significant enough to be meaningful as being a diagnostic marker for melanoma tumors. Thirdly, although, Dr. Polakis states that approximately 200 genes transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells, Dr. Polakis does not state how many proteins encoded by the 200 genes are expressed at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis does not state that the 30 "tumor antigen proteins" are expressed at significantly higher levels in human tumor cells than in corresponding normal human cells. Moreover, while Dr. Polakis bases his findings with reference to facts, the facts are not independently provided for the examiner to draw independent conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art provides strong evidence that increased mRNA levels do not correlate with increased protein levels in both healthy and cancerous tissues

(Gokman-Polar et al, Haynes et al, Gygi et al, Hanash [a] and Hanash et al [b]). Further, Dr. Polakis has an interest in the case since he is employed by the assignee. While the absolute certainty is not the legal standard for utility, a specific and substantial utility in reasonably confirmed and practical form is required for the claimed invention.

Appellants, along with the Grimaldi and Polakis declarations, Appellants also provide teachings from Molecular Biology of the Cell by Bruce Alberts and Genes VI (1997) by Benjamin Lewin, to support their assertion that there is a correlation between increased gene expression and increased protein expression (pages: 23-25 of the Brief). Appellants also refer to additional articles by Zhigang et al, and Meric et al as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Zhigang et al describe a specific example of the expression of prostrate stem cell antigen (PSCA) protein and mRNA to validate it as potential molecular target for diagnosis and treatment of human prostrate cancer. It is asserted that the data shows "a high degree of correlation between PSCA protein and mRNA expression". Further Meric et al states "the fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. Meric et al also teaches that most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Although, Appellants contend that the regulation is primarily at the transcriptional level (based on teachings found in Molecular Biology of the Cell), the prior art references discussed above teach that gene expression is quite complicated and is regulated at the level of

mRNA transcription, mRNA stability, mRNA translation and protein stability (e.g., Meric et al at page 971, left column, first paragraph of introduction). In addition, unlike the instant invention, Zhigang et al provide immunohistochemical analysis and mRNA hybridization to correlate the mRNA expression with the protein for a known prostate stem cell antigen (PSCA). Unlike the instant PRO1864 polypeptide, PSCA is well characterized and is a cell surface antigen that is predominantly prostate specific (see page 2). Further, the focus of efforts to exploit differences in gene expression at the level of mRNA between cancer cells and normal cells coincided with the advent of cDNA array technology, which facilitated this type of approach (Meric et al, p. 971, left column first paragraph of introduction). Also, reading of Meric et al seems to teach away from Appellants' claim that there is a direct correlation between increased mRNA levels and the level of expression of the encoded protein. For example, the reference discloses that variations in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974). In addition, comparisons of message and protein using proteomics, show a lack of correlation, as is evidenced by Gokman-Polar et al, Haynes et al and Gygi et al.

Appellants assert that declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references discussed establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and changes in the in the level of the encoded protein. It is the contention of the Appellants that substantial amount of evidence supporting their position has been provided and Appellants criticize the Examiner for not providing

adequate references to support the lack of utility. Appellant's arguments has been fully considered, but are not deemed to be persuasive for the reasons set forth immediately above. Therefore, considered as a whole, the overwhelming amount of evidence it is believed that the rejection should be sustained.

At the p. 26 of the Brief, Appellant argues that the asserted utility for PRO1864 as a cancer diagnostic is specific. The examiner agrees.

Appellants on pages 27-28 of the Brief argue that the Examiners response to the 1st Grimaldi declaration is not adequate and reminds the Examiner that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Further it is asserted "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being question." In addition, it is argued that declarations relating to issues of fact should not be summarily dismissed as "opinions' without adequate explanation of how the declaration fails to rebut the Examiners' position. Appellants further argue that the Examiner has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinions. Contrary to Appellants assertions that the Examiner has not supplied any reason or evidence in support of his position, the Examiner offered evidence from the literature which cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Hu et al., pages 6-7 of the Office Action dated 1/31/2005). In addition and as indicated above, Mr. Grimaldi has an interest in the case, since he is employed by the assignee. Finally, while Mr. Grimaldi bases his findings with reference to facts, the

facts are not independently provided for the examiner to draw independent conclusions. For example, it is not clear if any of the tumors were from skin or lung etc., or how highly amplified the genes were that correlated with polypeptide overexpression. Appellants also provide several patents in which apparently analogous fact pattern exists. As indicated by the Appellants themselves "... actions taken in other applications are not binding on the PTO with respect to the present application."

Appellants on pages 28-29 of the Brief argue that the Examiners arguments to second Grimaldi declaration fail to establish that one of skill in the art would doubt Appellants' asserted utility. Regarding the second Grimaldi declaration and as discussed above the PRO1864 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PRO1864 gene is known to occur. All that the specification demonstrates is that the PRO1864 nucleic acid (mRNA) was more highly expressed in melanomas compared to normal skin. No mutation or translocation of PRO1864 has been associated with skin cancer. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PRO1864 polypeptide is amplified in an unknown number of samples, and invite the artisan to determine the rest of the story. Even if the differential message expression can be used in the diagnosis of cancer, the lack of a nexus between the differential mRNA expression and polypeptide of PRO1864 or antibodies binding the polypeptide of PRO1864, make the rejections for lack of utility and enablement proper.

At page 29 of the Brief, Appellant comments upon the examiner's evaluation of the Polakis declaration. Specifically, Appellant argues that the Polakis declaration was submitted to support the position that there is a correlation between mRNA and polypeptide levels. Appellant reiterates that they have provided numerous references (discussed above) and the declaration of an additional expert, which indicates that it is well established that generally, there is a correlation between changes in mRNA level and changes in the level of the corresponding protein. Appellant contends that as discussed above the art of Gokman-Polar et al, Haynes et al and Gygi et al do not contradict Appellants' position that, in general, differential expression of mRNA correlates with differential expression of the encoded polypeptide. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. In the instant case, the nature of the fact sought to be established (1) is whether or not increased mRNA levels are predictive of increased polypeptide levels. The art provides strong evidence (2) that increased mRNA levels do not correlate with increased protein levels in both healthy and cancerous tissues. See Haynes et al, Gygi et al, Gokman-Polar et al, Hanash [a] and Hanash et al [b] (discussed supra). Additionally, Dr. Polakis has an interest in the case since he is employed by the assignee (3). Finally, while Dr. Polakis bases his findings with reference to facts, the facts are not independently provided for the

examiner to draw independent conclusions (4). For example, it is not clear if any of the tumors were from skin, or how highly amplified the genes were that correlated with polypeptide overexpression. Based on the totality of the evidence, it is maintained that one skilled in the art would view the instant differential mRNA expression data as merely preliminary with regard to whether or not protein levels of PRO1864 are differentially expressed in melanomas, are tumor-dependent, consistent and measureable. Further research would have to be done in order to determine if PRO1864 protein are differentially expressed and, if so, whether or not the differential expression is significant enough to reasonably confirm the usefulness of PRO1864 protein as a skin cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not substantial.

Appellants on pages 29-30 of the Brief respond to Examiners arguments with respect to the Alberts and Lewin references (cited as Exhibits 4-6 in Appellants response dated 5/2/05). Appellant asserts that the PTO does not address the teachings in Alberts that "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes" and "[f]or most genes transcriptional controls are paramount." Alberts at 379 (emphasis added). Appellant indicates that the PTO does not address the teachings in Lewin that "the overwhelming majority of regulatory events occur at the initiation of transcription." Lewin at 848 (emphasis added). The PTO does not provide a basis for failing to address evidence of the "overwhelming majority" and "paramount" controls of gene expression, and instead

focuses on other controls that can act later. Appellants assert that full consideration would lead to a conclusion that the "overwhelming majority" and "paramount" controls have a greater influence on gene expression than "other controls" that can act later. These arguments have been fully considered but are not deemed persuasive. While the examiner agrees with the teachings of Alberts and Lewin that initiation of transcription is the most common point for a cell to regulate gene expression, it is not the only means of regulating gene expression. As stated by Alberts (Exhibit 4, 1994), transcriptional control for most genes makes sense because only transcriptional control ensures that no superfluous intermediates are produced, however, Alberts indicates that, gene expression can be regulated at many steps in the pathway from DNA to RNA to protein and includes control of protein synthesis, mRNA degradation and protein activity control (i.e., processing and modification) (see page 403 and Fig 9-2). Additionally, Alberts (Exhibit 5, 2002) state: "the final level of a properly folded protein in a cell therefore depends upon the efficiency with which each of the many steps [from DNA to protein] is performed" (page 363, last full paragraph and page 364, Figure 6-90). Further, Lewin clearly states: "production of RNA cannot inevitably be equated with production of protein" (paragraph bridging pages 847-848). Therefore, given the paucity of information regarding PRO1864 expression in tumors and the evidence in the art that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would view the instant differential mRNA expression data as merely preliminary with regard to whether or not protein levels of PRO1864 are differentially expressed in

melanomas. Further research would have to be done in order to determine if the PRO1864 protein is differentially expressed and, if so, whether or not the differential expression is significant enough to reasonably confirm the usefulness of PRO1864 protein as a skin cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not substantial.

At pages 30-31 of the Brief Appellants review the Examiner's response to the Zhigang reference. Appellants reiterate that Zhigang reported that the correlation between mRNA expression and protein expression occurred in 93% of the samples tested. Appellants submit that there is no requirement to provide evidence sufficient to establish an asserted utility as a matter of statistical certainty. Appellant asserts that this standard is inconsistent with the Utility Guidelines and governing case law. This has been fully considered but is not found persuasive for the following reasons. It is acknowledged that Zhigang (Exhibit 7, dated 5/2/05) presents data showing a high degree of correlation between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence). However, exceptions were noted (paragraph bridging pages 3-4, page 4, left column, full paragraph 1), and, unlike Zhigang, Appellants have not provided any testing of PRO1864 polypeptide expression. The present application does not disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Further, experimentation would be required to identify or reasonably confirm a "real world" context of use. While the absolute certainty is not the legal standard for utility, a specific

and substantial utility in reasonably confirmed and practical form is required for the claimed invention.

Appellants argue extensively in pages 31-37 of the Brief that the courts have held that the utility requirement was satisfied in similar cases. Finally on page 38 of the Brief, Appellant concludes by stating that the instant specification discloses a specific, substantial and credible utility for the antibodies to the PRO1864 polypeptide as a diagnostic marker for cancer. The Examiner believes that the rejections should be sustained for the reasons set forth above.

(9b) Grounds of Rejection

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10b) Response to Arguments

Appellant refers to the arguments and information presented in response to the rejection under 35 U.S.C. 101 (see page 42 and the top of page 43 of the Brief). Appellant submits that the PRO1864 polypeptides have utility in the diagnosis of cancer. The Examiner believes that the rejection should be sustained for the reasons set forth above. Therefore, for reasons set forth above, Appellant's arguments and evidence have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility, enablement. As Appellants recognize, a rejection under 35 U.S.C. 112, first paragraph, may be maintained on the same basis as a lack of

utility rejection under 35 U.S.C 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

As an additional matter, Appellants Brief at pages 39-45 combines elements of the above enablement rejection created by the deficiency under 35 U.S.C 101 and the separate enablement rejection under 35 U.S.C. 112, first paragraph (see page 8 of the first Office Action dated 1/31/2005). It is noted that this separate enablement rejection is presently withdrawn by the Examiner to simplify the issues before the board (see item (6) of this Examiner's Answer).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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